IN THE CLAIMS: See Listing of Claims. This listing will replace all prior versions of claims in the application.

REMARKS

The Applicant acknowledges the Examiner's comprehensive Office Action with appreciation. The Office maintains the previously issued Restriction Requirement. Claims 37-74 remain pending in the application; however, Claims 37-55 and 62-65 are cancelled without prejudice to their further prosecution in a divisional application in response to the Restriction Requirement. The Office raises rejections under 35 USC § 101 and 35 USC § 112, first and second paragraphs. The Office also raises a rejection under 35 USC § 103.

Claim 56 is rejected under 35 USC § 101. With the instant Amendment, Claim 56 has been cancelled.

Claims 56-61, 66, and 70-74 are rejected for indefiniteness under 35 USC § 112, second paragraph. It is the position of the Office that the term "aminocyclohexane derivatives" recited in the claims is indefinite because it is not clear from the claims and/or specification which compounds are encompassed by this term. It is also the position of the Office that Claim 66 is indefinite because it refers to various substituted groups (e.g., substituted aryl, substituted alkyl, etc.) without defining which substituents are encompassed by the term "substituted."

With the instant Amendment, the 1-aminocyclohexane derivatives recited in Claims 57 and 72 have been defined as compounds of general formula (I), which compounds of general formula (I) were previously recited in Claim 66, and Claim 66 has been cancelled. Moreover, the "substituted groups" previously recited in the definition of general formula (I) (e.g., "substituted aryl", "substituted alkyl", etc.) have been deleted. Reconsideration and withdrawal of the indefiniteness rejection is respectfully requested.

Claims 56-61 and 66-74 are rejected for lack of enablement under 35 USC § 112, first paragraph. It is the position of the Office that the specification, while being enabling for compositions for treating specific dementias such as Alzheimer's disease, does not reasonably provide enablement for compositions for treating all dementias associated with a CNS disorder. It is the further position of the Office that the specification, while being enabling for compositions comprising the specific acetylcholinesterase inhibitors and aminocyclohexane derivatives disclosed in the specification, does not reasonably provide enablement for a combination of any acetylcholinesterase inhibitor and any aminocyclohexane derivative.

With the instant Amendment, pharmaceutical composition Claim 57 has been amended to delete the functional language "for treatment of a dementia associated with a CNS disorder" and pharmaceutical composition Claim 72 has been amended to delete the functional language "for treatment of dementia", since such functional language is not considered by the Office to have any patentable relevance in pharmaceutical composition claims, and Claims 60-61 have been cancelled.

As noted above with respect to the indefiniteness rejection, Claims 57 and 72 have also been amended to define the claimed 1-aminocyclohexane derivatives as compounds of general formula (I). Moreover, Claims 57 and 72 have also been amended to recite specific acetylcholinesterase inhibitors disclosed in the specification (i.e., galantamine, tacrine, donepezil, rivastigmine, huperzine A, zanapezil, ganstigmine, phenserine, phenethylnorcymserine (PENC), cymserine, thiacymserine, SPH 1371 (galantamine plus), ER 127528, RS 1259, and F3796), and Claim 71 has been cancelled. Support for this amendment may be found in the specification as pages 9 and 13. Thus, the Applicant respectfully submits that the scope of compounds encompassed by the instant combination pharmaceutical compositions is enabled by the specification.

Reconsideration and withdrawal of the lack of enablement rejections is respectfully requested.

Claims 56-61 and 66 -74 are rejected for obviousness under 35 USC § 103(a) based on Gold, et al. in view of Dooley, et al. It is the position of the Office that Gold, et al. disclose pharmaceutical compositions comprising the instant 1-aminocyclohexane derivatives which are useful in the treatment of neurodegenerative diseases, including Alzheimer's disease. The Office goes on to state that Gold, et al. also disclose pharmaceutical compositions comprising specific dosages (i.e., 10 mg and 12 mg) of active agent. The Office acknowledges that Gold, et al. do not disclose pharmaceutical compositions further comprising an acetylcholinesterase inhibitor.

It is the position of the Office that Dooley, et al. disclose that donepezil is a reversible acetylcholinesterase inhibitor which is indicated in the treatment of patients with mild to moderate Alzheimer's disease, and that the reference further discloses that a dose of 5 or 10 mg of donepezil per day significantly improved cognition in patients with mild to moderate Alzheimer's disease. The Office concludes that it would have been obvious to add 5 or 10 mg of donepezil to the pharmaceutical compositions of Gold, et al. to arrive at the instantly claimed compositions. The Office goes on to state that "[i]t has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose."

The Applicant respectfully submits that the study disclosed in instant Therapy Example 1 (which describes the results of a human clinical trial involving the combination of memantine and AChE inhibitors, i.e., representative examples of the instant combination) concludes that the instant combination results in clinical improvement, an observation not previously recorded in Alzheimer's therapy. This demonstrated improvement is an ***unexpected*** superadditive effect, which may not be inferred from the teaching in the art which never amounts to more than lessening the decline in an Alzheimer's disease patient. While previous AChE inhibitor and NMDA antagonist therapies have demonstrated functional improvement, no previous research was able to predict reversal, even though this was always a desired outcome. With this data, the instant inventor achieves a surprising result, which

result was never a reasonable expectation based on the speculation of the extant art.

Moreover, the Applicant provides two references, Reisberg, et al. (*N. Eng. J. Med.*, **2003**, *348*, 1333-1341) and Tariot, et al. (*JAMA*, **2004**, *291*, 317-324), which references are also listed on the accompanying Form PTO-1449, which disclose results providing further support for the surprising and unexpected results associated with the instant combination. Reisberg, et al. disclose a clinical study involving treatment of moderate to severe Alzheimer's patients with memantine. Tariot, et al. evaluate the clinical study which is the subject of instant Therapy Example 1 involving the treatment of moderate to severe Alzheimer's patients with memantine and donepezil or placebo and donepezil. Both studies use the Severe Impairment Battery (SIB) test (designed to measure cognitive performance in advanced Alzheimer's disease) to evaluate the efficacy of treatment.

Reisberg, et al. disclose data which demonstrate that memantine alone does not improve the SIB score but only reduces the decrease in SIB score, and Tariot, et al. evaluate similar data which demonstrate that donepezil alone also does not improve the SIB score but only reduces the decrease in SIB score. Tariot, et al. further evaluate data which demonstrate that the subject matter of the instant invention, namely a combination of memantine and donepezil, actually improves the SIB score. The evaluated data demonstrate that the instant combination leads to cognitive improvement and that these results are superior to the results that one skilled in the art would have expected with treatment employing either an NMDA receptor antagonist or an AChE inhibitor alone, as well as any additive effect which would have been expected on combination administration.

Thus, the Applicant respectfully submits that the instant combination is not rendered obvious by the disclosure of the cited references. Reconsideration and withdrawal of the obviousness rejection under 35 USC § 103 is respectfully requested.

Finally, with the instant Response, the Applicant also submits an Information Disclosure Statement which, it is respectfully submitted, should materially advance and accelerate the prosecution of the above-identified application. It is respectfully

requested that the information be expressly considered during the prosecution of this application and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

As will be noted, this Information Disclosure Statement calls a number of references, which might be considered relevant, to the attention of the Examiner. The fact that these references are in fact "Prior Art" is, however, not admitted.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR § 1.98 and the Examiner is respectfully requested to consider the listed references.

* * * * *

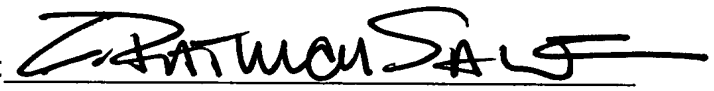
Accordingly, entry of the present amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: 

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Enclosure: Form PTO-1449 and Accompanying References; Check No. 75455 for IDS Fee; Check No. 75454 for One (1) Month Extension Fee; Listing of Claims; and Postal Card Receipt

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THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.